Supplementary Online Content

Supplementary Methods 1. Disease Risk Score Analysis

Disease Risk Score Analysis (DRS) was conducted, utilizing a historical cohort to address residual confounding.[1] This is analogous to the propensity score, and has been shown to have a comparable performance.[2,3] Using the same study inclusion criteria for the primary analyses, a cohort of patients newly prescribed antihypertensive medications from January 1 1990 and December 31st 1994 was first identified. A Cox proportional hazards model was fitted that included all potential baseline confounders listed in the manuscript (excluding statin use and tuberculosis diagnosis due to a low number of events). The disease risk score was then calculated in the historical cohort by taking the products of the regression coefficients and the individual covariate values (but where the exposure status was set to zero), and summing these products for each patient. Hazard ratios of lung cancer were estimated by comparing use of ACEIs with use of ARBs by stratifying the Cox proportional hazards model on DRS deciles.

References

1. Glynn, Gagne & Schneeweiss. Role of disease risk score in comparative effectiveness research with emerging therapies. Pharmacoepidemiol Drug Saf 2012; 21(s2):138-147

2. Arbogast PG, Ray WA. Performance of disease risk scores, propensity scores, and traditional multivariable outcome regression in the presence of multiple confounders. Am J Epidemiol. 2011;174(5):613-620. doi:10.1093/aje/kwr143.

3. Arbogast PG, Ray WA. Use of disease risk scores in pharmacoepidemiologic studies. Stat Methods Med Res. 2009;18(1):67-80. Doi:10.1177/0962280208092347.

Supplementary Methods 2. Marginal Structural Cox Proportional Hazards Model.

We conducted a marginal structural Cox proportional hazards model to address potential residual time-dependent confounding over the 21-year follow-up period. This method is designed to adjust for time-dependent confounding associated with time-varying exposures.[1,2] Two pooled logistic regression models were fitted to estimate the conditional probability of being exposed to ACEIs at 30-day intervals during follow-up; one for the numerator and one for the denominator of the stabilized inverse-probability-of-treatment weights (IPTWs). The numerator treatment model included baseline covariates (the covariates included in the primary analysis, listed in the main text) and follow-up time. The denominator model included covariates (the same as those listed in the main text) measured at each time interval and follow-up time. In both the numerator and denominator models, follow-up time was modelled using a restricted cubic spline with five knots to reduce bias due to model misspecification from linearity assumptions.[3] We also estimated inverse probability of censoring weights (IPCWs) in a similar fashion. Stabilized IPTW and IPCW for each patient in the cohort were computed using the predictive probabilities from both treatment and censoring models. The product of these stabilized IPTWs and IPCWs was then used to reweight the cohort, in which we estimated the marginal HR of lung cancer associated with ACEI use, with 95% confidence intervals, calculated using robust variance estimators.[2]

References

1. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550–60.

2. Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology 2000;11:561–70.

3. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol 2008;168:656–64. doi:10.1093/aje/kwn164

Supplementary Table A Read Codes for Lung Cancer Diagnosis

Read Code	Read Term
B22z.11	Lung cancer
B22z.00	Malignant neoplasm of bronchus or lung NOS
B907200	Neoplasm of uncertain behaviour of lung
H58y400	Squamous metaplasia of lung
BB1K.00	[M]Oat cell carcinoma
B222.00	Malignant neoplasm of upper lobe, bronchus or lung
B224100	Malignant neoplasm of lower lobe of lung
B221.00	Malignant neoplasm of main bronchus
B22..00	Malignant neoplasm of trachea, bronchus and lung
B221000	Malignant neoplasm of carina of bronchus
B224000	Malignant neoplasm of lower lobe bronchus
B222.11	Pancoast's syndrome
B221z00	Malignant neoplasm of main bronchus NOS
B222100	Malignant neoplasm of upper lobe of lung
B224.00	Malignant neoplasm of lower lobe, bronchus or lung
B223.00	Malignant neoplasm of middle lobe, bronchus or lung
B222000	Malignant neoplasm of upper lobe bronchus
B221100	Malignant neoplasm of hilus of lung
B225.00	Malignant neoplasm of overlapping lesion of bronchus & lung
B22y.00	Malignant neoplasm of other sites of bronchus or lung
B223100	Malignant neoplasm of middle lobe of lung
Byu2000	[X]Malignant neoplasm of bronchus or lung, unspecified
B223000	Malignant neoplasm of middle lobe bronchus
B224z00	Malignant neoplasm of lower lobe, bronchus or lung NOS
B222z00	Malignant neoplasm of upper lobe, bronchus or lung NOS
B223z00	Malignant neoplasm of middle lobe, bronchus or lung NOS

Supplementary Table B. Adjusted HRs for the Association between the Use of ACEI and the Risk of Lung Cancer (Interaction with Smoking)[*]

	Never smoker	Former smoker	Current smoker
ARBs	1.00 (reference)	1.00 (reference)	1.00 (reference)
ACEIs	1.29 (0.96 to 1.73)	1.07 (0.86 to 1.34)	1.13 (0.94 to 1.36)
			p-interaction: 0.40

Abbreviations: HR, hazard ratio; CI, confidence interval; ACEI, Angiotensin converting enzyme inhibitors; ARB, Angiotensin receptor blockers

[*] Adjusted for age, sex, year of cohort entry, body mass index, smoking, alcohol-related disorders (including for example alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and hepatic flexure), history of lung diseases prior to cohort entry (including pneumonia, tuberculosis, and history of chronic obstructive pulmonary disease), duration of treated hypertension, use of statins, and the total number of unique drug classes in the year before cohort entry.

Supplementary Table C. Crude and Adjusted HRs for the Association Between the Use of ACEIs and the Risk of Lung Cancer among Non-Smokers

Exposure[†]	Events	Person-years	Incidence rate (95% CI)[*]	Crude HR	Adjusted HR (95% CI)[‡]
ARBs	39	112,137	0.3 (0.2 to 0.5)	1.00 [Reference]	1.00 [Reference]
ACEIs	408	944,327	0.4 (0.4 to 0.5)	1.27	1.18 (0.85 to 1.65)
Duration of ACEIs use, years					
≤ 5	240	689,872	0.3 (0.3 to 0.4)	1.10	1.03 (0.74 to 1.45)
5.1-10	134	215,890	0.6 (0.5 to 0.7)	1.57	1.45 (1.01 to 2.08)
> 10	34	38,566	0.9 (0.6 to 1.2)	1.89	1.64 (1.02 to 2.64)
Time since first ACEI use, years					
≤ 5	179	553,406	0.3 (0.3 to 0.4)	1.06	1.01 (0.71 to 1.43)
5.1-10	164	308,157	0.5 (0.5 to 0.6)	1.43	1.32 (0.93 to 1.88)
> 10	65	82,765	0.8 (0.6 to 1.0)	1.72	1.49 (0.98 to 2.25)

Abbreviations: HR, hazard ratio; CI, confidence interval; ACEI, Angiotensin converting enzyme inhibitors; ARB, Angiotensin receptor blockers

[*] Per 1000 Person-Years.

[†] Use of other antihypertensive drugs is considered in the model, but not presented in the table.

[‡] Adjusted for age, sex, year of cohort entry, body mass index, smoking, alcohol-related disorders (including for example alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and hepatic flexure), history of lung diseases prior to cohort entry, including pneumonia, tuberculosis, and history of chronic obstructive pulmonary disease, duration of treated hypertension, use of statins, and the total number of unique drug classes in the year before cohort entry.

Supplementary Table D. Crude and Adjusted HRs for the Association Between the Use of ACEI and the Risk of Lung Cancer (Varying the Lag Period to 2 years)

Exposure †	Events	Person-years	Incidence rate (95% CI)*	Crude HR	Adjusted HR (95% CI) ‡
ARBs	245	185,766	1.3 (1.2 to 1.5)	1.00 [Reference]	1.00 [Reference]
ACEIs	2792	1,659,614	1.7 (1.6 to 1.7)	1.29	1.13 (0.99 to 1.29)

Abbreviations: HR, hazard ratio; CI, confidence interval; ACEI, Angiotensin converting enzyme inhibitors; ARB, Angiotensin receptor blockers

* Per 1000 Person-Years.

† Use of other antihypertensive drugs is considered in the model, but not presented in the table.

‡ Adjusted for age, sex, year of cohort entry, body mass index, smoking, alcohol-related disorders (including for example alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and hepatic flexure), history of lung diseases prior to cohort entry (including pneumonia, tuberculosis, and history of chronic obstructive pulmonary disease), duration of treated hypertension, use of statins, and the total number of unique drug classes in the year before cohort entry

Supplementary Table E. Crude and Adjusted HRs for the Association Between the Use of ACEI and the Risk of Lung Cancer (Varying the Lag Period to 3 years)

Exposure †	Events	Person-years	Incidence rate (95% CI)*	Crude HR	Adjusted HR (95% CI) ‡
ARBs	210	160,174	1.3 (1.1 to 1.5)	1.00 [Reference]	1.00 [Reference]
ACEIs	2396	1,375,795	1.7 (1.7 to 1.8)	1.34	1.18 (1.02 to 1.35)

Abbreviations: HR, hazard ratio; CI, confidence interval; ACEI, Angiotensin converting enzyme inhibitors; ARB, Angiotensin receptor blockers

* Per 1000 Person-Years.

† Use of other antihypertensive drugs is considered in the model, but not presented in the table.

‡ Adjusted for age, sex, year of cohort entry, body mass index, smoking, alcohol-related disorders (including for example alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and hepatic flexure), history of lung diseases prior to cohort entry (including pneumonia, tuberculosis, and history of chronic obstructive pulmonary disease), duration of treated hypertension, use of statins, and the total number of unique drug classes in the year before cohort entry

Supplementary Table F. Crude and Adjusted HRs for the Association Between the Use of ACEI and the Risk of Lung Cancer
(Disease Risk Score Analysis)

Exposure †	Events	Person-years	Incidence rate (95% CI)*	Crude HR	Adjusted HR (95% CI) ‡
ARBs	266	213,557	1.2 (1.1 to 1.4)	1.00 [Reference]	1.00 [Reference]
ACEIs	3186	1,977,139	1.6 (1.6 to 1.7)	1.32	1.20 (1.06 to 1.36)

Abbreviations: HR, hazard ratio; CI, confidence interval; ACEI, Angiotensin converting enzyme inhibitors; ARB, Angiotensin receptor blockers
* Per 1000 Person-Years.
† Use of other antihypertensive drugs is considered in the model, but not presented in the table.
‡ Stratified on disease risk score decile. Variables included in the disease risk score included; age, sex, year of cohort entry, body mass index, smoking, alcohol-related disorders (including for example alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and hepatic flexure), history of lung diseases prior to cohort entry (including pneumonia and history of chronic obstructive pulmonary disease), duration of treated hypertension and the total number of unique drug classes in the year before cohort entry.

Supplementary Table G. Crude and Adjusted HRs for the Association Between the Use of ACEI and the Risk of Lung Cancer (Marginal Structural Model)

Exposure †	Events	Person-years	Incidence rate (95% CI)*	Crude Marginal HR	Adjusted Marginal HR (95% CI)‡
ARBs	266	218,312	0.1 (0.09 to 0.1)	1.00 [Reference]	1.00 [Reference]
ACEIs	3186	2,023,733	0.1 (0.1 to 0.1)	1.44	1.22 (1.03 to 1.44)

Abbreviations: HR, hazard ratio; CI, confidence interval; ACEI, Angiotensin converting enzyme inhibitors; ARB, Angiotensin receptor blockers

* Per 1000 Person-Months.

† Use of other antihypertensive drugs is considered in the model, but not presented in the table.

‡ Adjusted for age, sex, year of cohort entry and the total number of unique drug classes in the year before cohort entry. Time updated variables included body mass index, smoking, alcohol-related disorders (including for example alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and hepatic flexure), history of lung diseases (including pneumonia, tuberculosis, and history of chronic obstructive pulmonary disease), duration of treated hypertension and use of statins.

Supplementary Table H. Crude and Adjusted HRs for the Association Between the Use of ACEI and the Risk of Lung Cancer (Using Thiazide Diuretic Use as an Alternative Comparator Group)

Exposure [†]	Events	Person-years	Incidence rate [*] (95% CI)	Crude HR	Adjusted HR (95% CI) [‡]
Thiazide diuretics	1511	1,074,713	1.4 (1.3 to 1.5)	1.00 [Reference]	1.00 [Reference]
ACEIs	3186	1,977,139	1.6 (1.6 to 1.7)	1.12	1.06 (1.00 to 1.13)
Cumulative Duration of ACEI use (years)					
≤ 5	2084	1,440,232	1.4 (1.4 to 1.5)	1.06	1.03 (0.96 to 1.10)
5.1-10	905	457,309	2.0 (1.9 to 2.1)	1.22	1.14 (1.04 to 1.24)
> 10	197	79,598	2.5 (2.1 to 2.8)	1.38	1.23 (1.04 to 1.44)

Abbreviations: HR, hazard ratio; CI, confidence interval; ACEI, Angiotensin converting enzyme inhibitors; ARB, Angiotensin receptor blockers

[*] Per 1000 Person-Years.

[†] Use of other antihypertensive drugs is considered in the model, but not presented in the table.

[‡] Adjusted for age, sex, year of cohort entry, body mass index, smoking, alcohol-related disorders (including for example alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and hepatic flexure), history of lung diseases prior to cohort entry (including pneumonia, tuberculosis, and history of chronic obstructive pulmonary disease), duration of treated hypertension, use of statins, and the total number of unique drug classes in the year before cohort entry.

Supplementary Table I. Crude and Adjusted HRs for the Association Between the Use of ARBs Compared to Thiazide Diuretics and the Risk of Lung Cancer

Exposure [†]	Events	Person-years	Incidence rate (95% CI)[*]	Crude HR	Adjusted HR (95% CI)[‡]
Thiazide diuretics	1511	1,074,713	1.4 (1.3 to 1.5)	1.00 [Reference]	1.00 [Reference]
ARBs	266	213,557	1.2 (1.1 to 1.4)	0.85	0.93 (0.82 to 1.06)
Cumulative duration of ARB use (years)					
≤ 5	173	144,546	1.2 (1.0 to 1.4)	0.88	0.97 (0.83 to 1.14)
5.1-10	78	59,047	1.3 (1.0 to 1.6)	0.79	0.86 (0.69 to 1.09)
> 10	15	9964	1.5 (0.8 to 2.5)	0.80	0.83 (0.50 to 1.39)

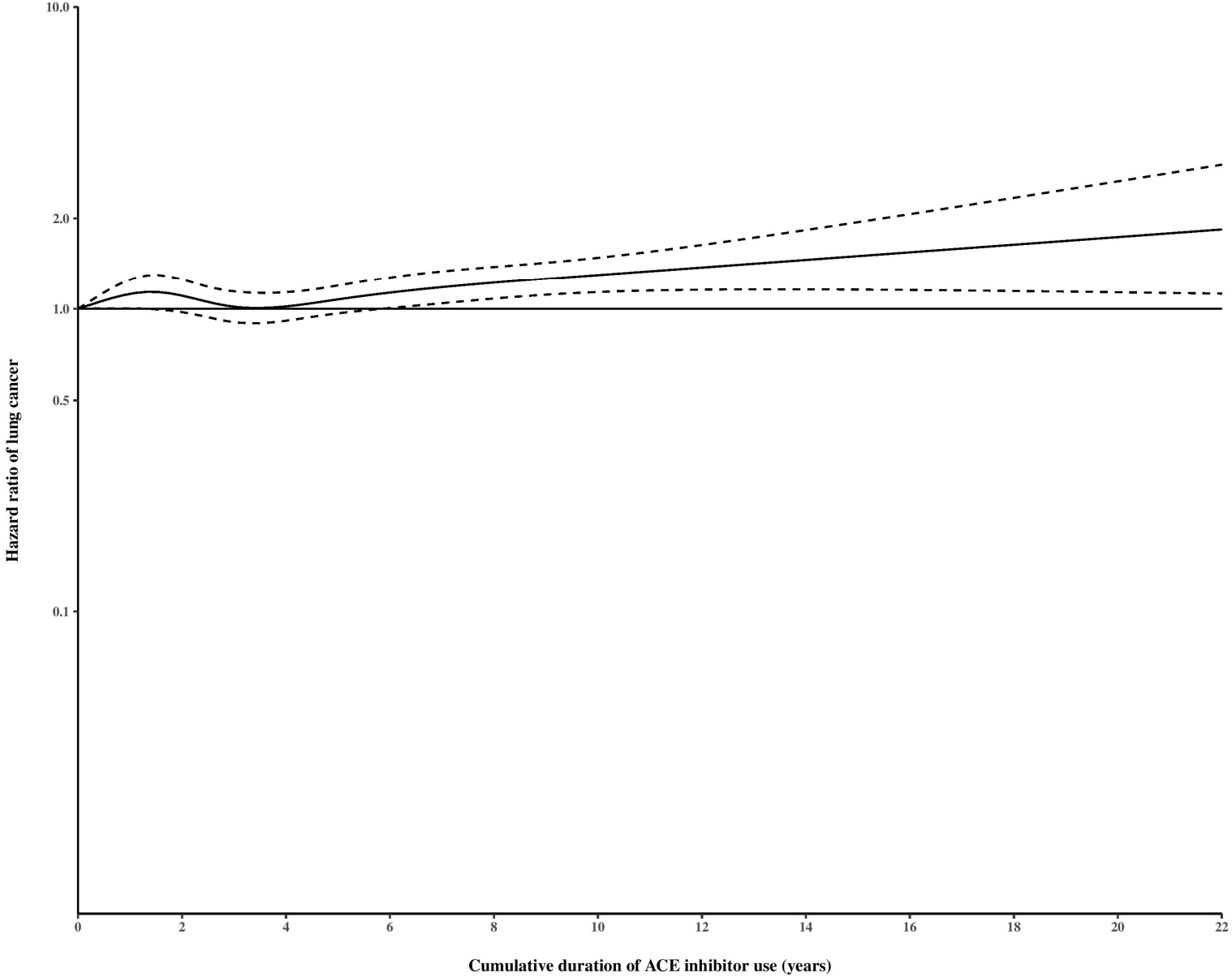
Abbreviations: HR, hazard ratio; CI, confidence interval; ACEI, Angiotensin converting enzyme inhibitors; ARB, Angiotensin receptor blockers

[*] Per 1000 Person-Years.

[†] Use of other antihypertensive drugs is considered in the model, but not presented in the table.

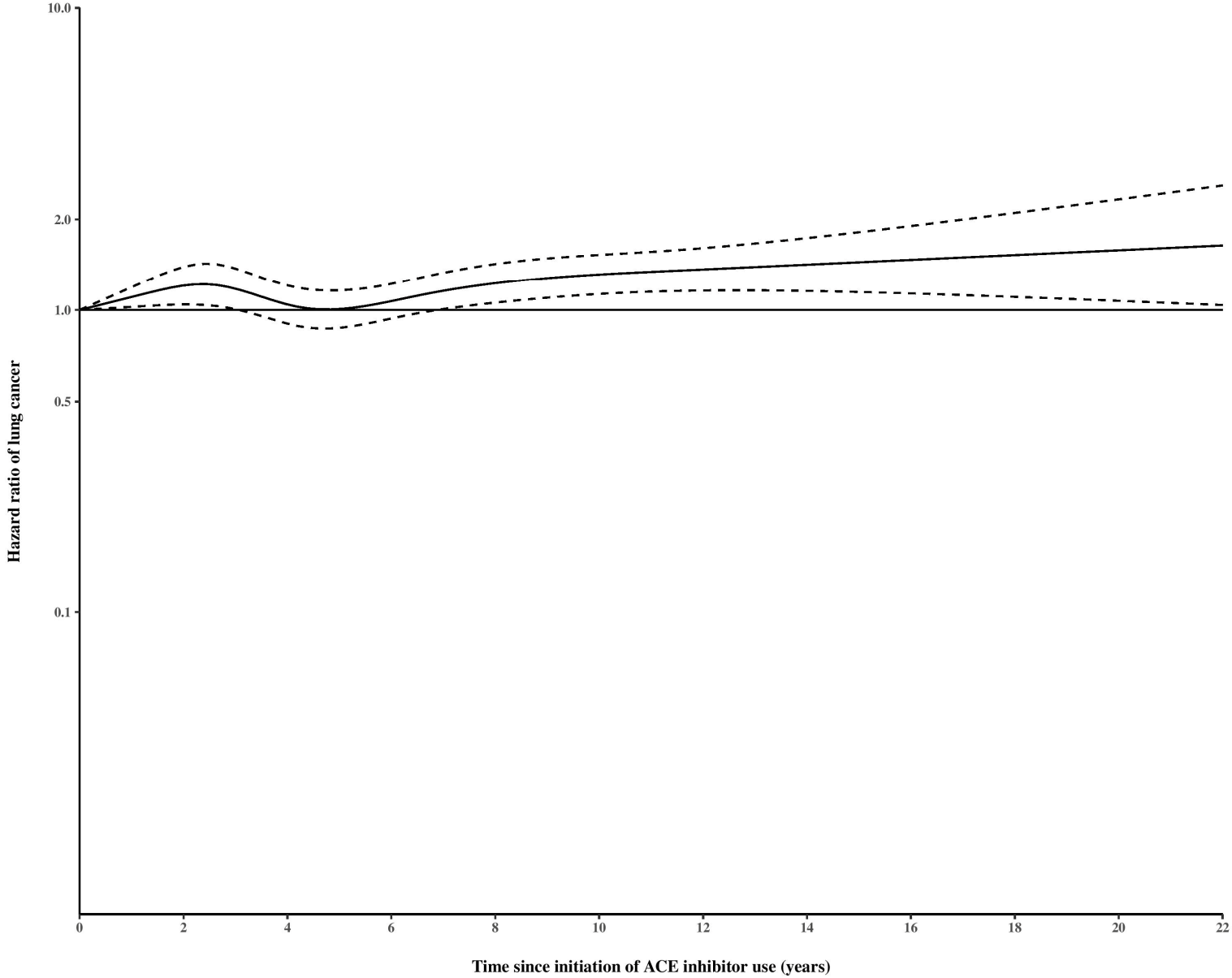
[‡] Adjusted for age, sex, year of cohort entry, body mass index, smoking, alcohol-related disorders (including for example alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and hepatic flexure), history of lung diseases prior to cohort entry (including pneumonia, tuberculosis, and history of chronic obstructive pulmonary disease), duration of treated hypertension, use of statins, and the total number of unique drug classes in the year before cohort entry

Supplementary Figure A



Smooth restricted spline curve of adjusted hazard ratio of lung cancer (solid line) and 95% confidence limits (dashed lines) as function of cumulative duration of ACEI use

Supplementary Figure B



Smooth restricted spline curve of adjusted hazard ratio of lung cancer (solid line) and 95% confidence limits (dashed lines) as function of time since ACEI initiation